PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 501/34

A1

(11) International Publication Number: **WO 99/35149**

(43) International Publication Date: 15 July 1999 (15.07.99)

(21) International Application Number: PCT/EP99/00057

(22) International Filing Date: 7 January 1999 (07.01.99)

(30) Priority Data:
A21/98 9 January 1998 (09.01.98) AT

(71) Applicant *(for all designated States except US)*: BIOCHEMIE GESELLSCHAFT MBH [AT/AT]; A–6250 Kundl (AT).

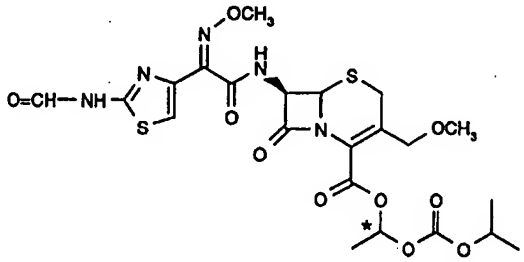
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: GREIL, Julia [AT/AT]; Lende 179 b, A–6233 Kramsach (AT). LUDESCHER, Johannes [AT/AT]; Kleinsoell 101, A–6252 Breitenbach (AT). TOTSCHNIG, Klaus [AT/AT]; Biochemiestrasse 44, A–6250 Kundl (AT). WOLF, Siegfried [US/US]; Bruggerstrasse 4, A–6230 Brixlegg (US).

(74) Agent: BECKER, Konrad; Novartis AG, Patent– und Markenabteilung, Lichtstrasse 35, CH–4002 Basel (CH).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PROCESS FOR THE PREPARATION OF CEFPODOXIME PROXETIL DIASTEREOISOMERS



(I)

(57) Abstract

A process for the adjustment of the diastereoisomeric ratio of a mixture of diastereoisomers of a compound of formula (I) the diastereoisomers being with respect with the carbon atom marked with a star in formula (I), comprising treating a compound of formula (I) with alcohol and water and use of that process in the production of cefpodoxime proxetil in a desired diastereoisomeric ratio, e.g. 0.5 to 0.6.

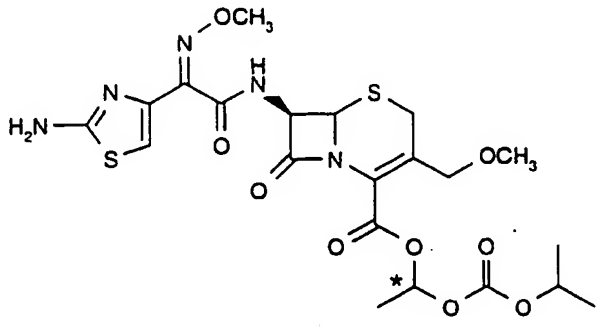
FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

PROCESS FOR THE PREPARATION OF CEFPODOXIME PROXETIL DIASTEREOISOMERS

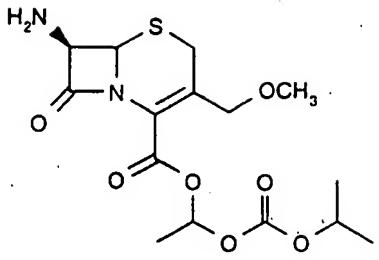
The present invention relates to cefpodoxim proxetil of formula



II

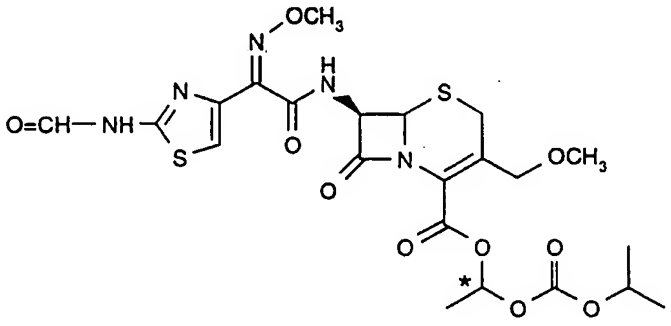
e.g. described in The Merck Index, Twelth Edition, Item 1991; and more particulary to a process for the adjustment, e.g. change, of the diastereoisomeric ratio of the two existing diastereoisomers being with respect to the carbon atom attached to the oxygen of the ester group in the carboxyl ester group in position 4 of the ring system (marked with a star (*) in formula II). A diastereoisomeric ratio (B/A+B) of cefpodoxime proxetil currently on the market may be around 0.53. B is the more apolar of the two diastereoisomers. Because of different bioavailability of these individual diastereoisomers a commercial form for oral administration of cefpodoxim proxetil has to be within a defined ratio (B/A+B); otherwise such a form might not be bioequivalent. A diastereoisomeric ratio (B/A+B) of 0.5 to 0.6 has been found to be bioequivalent with a commercial form. Determination of the diasterisomeric content of the diastereoisomers A and B in cefpodoxime proxetil may be carried out by HPLC, e.g. as described in Pharmacopeial Forum, Vol. 23, No. 4, p. 4388 ff (1997), the content of which is incorporated herein by reference, from which a diastereoisomeric ratio (B/A+B) and (A/A+B) may be calculated.

One process in the production of cefpodoxime proxetil may be carried out via acylation of 7-amino-3-methoxy-methyl-3-cephem-4-carboxylic acid-1-(isopropoxycarbonyloxy)ethylester of formula



III

with activated Z-2-(methoxyimino)-2-(2-formylaminothiazol-4-yl)-acetic acid to obtain N-formylcefpodoxime proxetil of formula



I

It was found that a mixture of diastereoisomers of a compound of formula I may be obtained in a diastereoisomeric ratio (B/A+B) of 0.48 to below 0.50. The reaction for splitting off the formyl group in a compound of formula I obtained to obtain cefpodoxime proxetil of formula II may have no significant influence on the diastereisomeric ratio (B/A+B) and consequently (B/A+B) in cefpodoxime proxetil obtained may be outside of 0.5 to 0.6 . Surprisingly a simple process has now be found wherein an appropriate diastereoisomeric ratio of the diastereoisomers of a compound of formula I may be obtained which may result in cefpodoxime proxetil by splitting off the formyl group in a diastereoisomeric ratio which is 0.5 to 0.6.

In one aspect the present invention provides a process for the adjustment, e.g. change, of the diastereoisomeric ratio (B/A+B), wherein B is the more apolar of the two diastereoisomers, of a mixture of diastereoisomers of a compound of formula I, e.g. adjusting a diastereoisomeric ratio (B/A+B) to 0.5 to 0.6; the diastereoisomers being with respect with the carbon atom marked with a star in formula I, comprising treating a mixture of diastereoisomers of a compound of formula I, e.g. in an additive, e.g. a compound selected from an organic amide, an urea, an imidazolidinone or a pyrimidinone, e.g. a 10 to 50 % (w/w) solution of a

mixture of diastereoisomers of a compound of formula I in an additive; with alcohol, e.g. selecting the alcohol from (C_{1-6})alcohols; and water, e.g. treating a mixture of diastereoisomers of a compound of formula I with 3 ml to 10 ml alcohol and 10 ml to 30 ml water per gram of a compound of formula I.

A process according to the present invention may be carried out as follows:
A compound of formula I may be produced, e.g. in conventional manner and e.g. as follows: The carboxylic acid group in position 4 of the ring system of 7-amino-3-methoxymethyl-3-cephem-4-carboxylic acid (AMCA) which is a known compound and obtainable e.g. in conventional manner, may be esterified to obtain a compound of formula III. This may be effected e.g. in conventional manner, e.g. by reacting AMCA with a compound of formula

$$X\text{-}CH\text{-}(CH_3)\text{-}O\text{-}CO\text{-}O\text{-}CH(CH_3)_2$$

wherein X denotes a leaving group, e.g. a conventional leaving group, such as a halogenide, e.g. an iodide; e.g. in the presence of a solvent. Esterification may be effected e.g. in a conventional solvent, e.g. an organic solvent such as ketones, e.g. acetone, e.g. in the presence of a hydrocarbon, e.g. toluene; and e.g. in the presence of a base; e.g. an amidine, such as 1,5-diazabicyclo(4,3,0)non-5-ene (DBN) and 1,8-diazabicyclo(5,4,0)undec-7-ene (DBU); or a guanidine, e.g. a linear guanidine, such as tetramethylguanidine, pentamethylguanidine, tetraethylguanidine, tetramethylethylguanidine and tetramethylbenzylguanidine or a cyclic or bicyclic guanidine, e.g. 1,5,7-triazabicyclo-(4,4,0)-dec-5-ene, and 7-methyl, 7-ethyl, 7-benzyl and 7-phenyl derivatives thereof. A compound of formula III obtained may be isolated, if desired, e.g. in conventional manner.

The nitrogen atom in position 7 of the ring structure of a compound of formula III, e.g. obtained as described above, e.g. with or without isolation, preferably without isolation, may be acylated e.g. in conventional manner. This may be effected e.g.by reaction of a compound of formula III obtained in in the esterifcation reaction, with activated Z-(2-formamidothiazol-4-yl)-methoxyimino acetic acid, e.g. including an ester and an acid halogenide, such as Z-(2-formylaminothiazol-4-yl)-methoxyimino-acetic acid chloride, e.g. in the form of a salt, e.g. a hydrochloride, including activated Z-(2-formamidothiazol-4-yl)-methoxyimino acetic acid obtainable by a Vilsmeier reaction. Vilsmeier activated Z-(2-formamidothiazol-4-yl)-methoxyimino acetic acid may be produced e.g. in conventional manner, e.g. in situ in the reaction mixture e.g. by treating Z-(2-formamidothiazol-4-yl)-methoxyimino acetic acid with phosphoroxyhalogenide, e.g. chloride, e.g. under Vilsmeier reaction conditions.

Acylation may be carried out in an organic solvent, including e.g. carboxylic acid esters, e.g. acetates, such as ethyl acetate; halogenated hydrocarbons, e.g. aliphatic, such as methylene chloride; e.g. in the presence of an amide, e.g. N,N-dimethylformamide; e.g. in the presence of pH adjustment. pH adjustment may be effeted e.g. by addition of a base, such as an inorganic base, e.g. a carbonate or bicarbonate, e.g. sodium and potassium, or e.g. of an, e.g. weakly, basic anionic exchange resin, to a pH of ca. 2.5 to 8.0. A compound of formula I obtained may be isolated, e.g. in conventional manner. A mixture of diastereoisomers of a compound of formula I may be obtained in a diastereoisomeric ratio (B/B+A) of 0.47 up to below 0.5.

For adjustment, e.g. change, of the diastereoisomeric ratio of a mixture of diastereoisomers of a compound of formula I, e.g. obtained as described above, e.g. with or without isolation, preferably without isolation, e.g. a reaction mixture from acylation, e.g. as described above, may be treated with alcohol and water, e.g. in the presence of an additive, e.g. a compound which is liquid under the reaction conditions and wherein a compound of formula I may be dissolved, e.g. a compound selected from an organic amide, e.g. an amide of formic acid or acetic acid, or a cyclic amide, e.g. pyrrolidone or N-methylpyrrolidone, or an urea, e.g. tetramethylurea, or an imidazolidinone, e.g.1,3-dimethyl-2-imidazolidinone (DMEU) or a pyrimidinone, e.g.1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), or a mixture of individual additives, e.g. as described above, preferably an organic amide or an urea. An additive may be added to a reaction mixture obtained in the acylation step. From a reaction mixture obtained in the acylation step, e.g. containing an additive, e.g. added after acylation reaction to the reaction mixture, a solvent used in the acylation step which is different from an additive described above may be evaporated off, e.g. keeping the main part of an additive in the evaporation residue.

A reaction mixture obtained in the acylation step or an evaporation residue as referred to hereinafter, e.g. obtainable e.g. as described above may be a solution, an, e.g. 10 to 50 % (w/w) solution, of a mixture of diastereoisomers of a compound of formula I in an additive, containing e.g. water, e.g. small amounts, e.g. originating from the acylation step, and e.g. containing amounts of organic solvent, e.g. other than an additive, e.g. organic solvent as used in the esterification and/or acylation step, e.g. from trace amounts up to 30% (w/w) in respect with a compound of formula I, e.g. depending whether, or in which extent, an evaporation step is used.

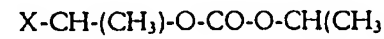
A reaction mixture obtained in the acylation step, or an evaporation residue obtained as described above, may be treated with water and alcohol, e.g. adding, e.g. dropwise or e.g. by allowing to flow

- an evaporation residue or a reaction mixture obtained in the acylation step to, e.g. into, a mixture of alcohol/water, or
- a mixture of alcohol/water to, e.g. into, an evaporation residue or a reaction mixture obtained in the acylation step, or
- an evaporation residue or a reaction mixture obtained in the acylation step to, e.g. into, alcohol; or alcohol to, e.g. into, an evaporation residue or a reaction mixture obtained in the acylation step; and adding, e.g. dropwise, water to, e.g. into, the mixture obtained; or adding the mixture obtained to, e.g. into, water.

Appropriate alcohols include e.g. (C_{1-6})alcohols, preferably methanol and ethanol and mixtures of individual alcohols. An appropriate amount of alcohol includes preferably an amount of 3 to 10 ml, e.g. 5 to 6 ml of alcohol per gram of a compound of formula I. An appropriate amount of water includes an amount which is greater than 5 ml, e.g. 10 to 30 ml per gram of a compound of formula I.

A compound of formula I may precipitate, e.g. in amorphous, e.g. filterable form. The diastereoisomeric ratio (B/B+A) of a mixture of diastereoisomers of a compound of formula I obtained may be dependent on the alcohol/water ratio in the mixture and may increase with increasing amounts of alcohol in respect with water. An alcohol/water ratio of about 1:1 to 1:6, preferably; 1:1.5 to 1:5 may conveniently be used to obtain a mixture of diastereoisomers wherein the diastereoisomeric ratio (B/B+A) is at least 0.5 and more.

In another aspect the present invention provides a process for the production of a mixture of diastereoisomers of cefpodoxim proxetil of formula II in a diastereoisomeric ratio (B/A+B), wherein B is the more apolar of the two diastereoisomers, of 0.5 to 0.6, the diastereoisomers being with respect with the carbon atom marked with a star in formula II, comprising producing a mixture of diastereoisomers of a compound of formula I, e.g. in a diastereoisomeric ratio of below 0.5, by acylating a compound of formula III, e.g. a mixture of diastereoisomers of a compound of formula III, e.g. produced by esterifying 7-amino-3-methoxymethyl-3-cephem-4-carboxylic acid with a compound of formula



wherein X denotes a leaving group;
with activated Z-(2-formamidothiazol-4-yl)-methoxyimino acetic acid,
treating a mixture of diastereoisomers of a compound of formula I in an additive e.g. a compound selected from an organic amide, an urea, an imidazolidinone or a pyrimidinone, e.g. a 10 to 50 % (w/w) solution of a mixture of diastereoisomers of a compound of formula I in an additive; with alcohol, e.g. selected from (C_{1-6})alcohols, and water, e.g. treating a mixture of diastereoisomers of a compound of formula I with 3 ml to 10 ml alcohol and 10 ml to 30 ml water per gram of a compound of formula I; and splitting off the formyl group from the amino group attached to the thiazolyl group.

In another aspect the present invention provides a process for the production of a mixture of diastereoisomers of cefpodoxim proxetil of formula II in a diastereoisomeric ratio (B/A+B), wherein B is the more apolar of the two diastereoisomers, of 0.5 to 0.6, the diastereoisomers being with respect with the carbon atom marked with a star in formula II, characerized by the follwing steps

i) esterifying 7-amino-3-methoxymethyl-3-cephem-4-carboxylic acid with a compound of formula

$$X\text{-}CH\text{-}(CH_3)\text{-}O\text{-}CO\text{-}O\text{-}CH(CH_3)_2$$

wherein X denotes a leaving group in the presence of a solvent, e.g. and in the presence of a base;

ii) acylating the amine group in position 7 of the ring system of a compound of formula III obtained in step i) with activated Z-(2-formamidothiazol-4-yl)-methoxyimino acetic acid, e.g. a halogenide, e.g. in the presence of a base;

iii) adding a compound selected from an organic amide, an urea, an imidazolidinone or a pyrimidinone to a reaction mixture obtained in step ii) and evaporating off a solvent used in the acylation step, and

iv) treating the evaporation residue obtained in step iii) with alcohol and water.

In a further aspect the present invention provides a process for the isolation of 7-[2-(2-formylaminothiazol-4-yl)-2-(Z)-(methoxyimino)-acetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(isopropoxy-carbonyloxy)-ethylester (as a diastereoisomeric mixture) of formula I; e.g. after the reaction of the compound of formula III with activated derivative of Z-2-(methoxyimino)-2-(2-formylaminothiazol-4-yl)-acetic acid in a solvent, characterised in that to the solution of the compound of formula I is added an organic amide, a urea, 1,3-dimethyl-2-imidazolidinone (DMEU) or 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone

(DMPU), the solvent is subsequently removed by evaporation and the residue of evaporation is mixed with water/alcohol.

A process according to the present invention is useful for the production of cefpodoxime proxetil in a diastereoisomeric ratio (B/A+B), wherein B is the more apolar of the two diastereoisomers, of 0.5 to 0.6. A diastereoisomeric ratio (B/A+B) of 0.5 to 0.6 of cefpodoxime proxetil, e.g. in a pharmaceutical composition, is bioequivalent to cefpodoxime proxetil, e.g. in a pharmaceutical composition, currently on the market. Cefpodoxime proxetil produced according to the present invention may thus be used in the same dosages and in the same indications as cefpodoxime proxetil currently on the market.

In the following examples, which illustrates the invention more fully, but should in no way limit its scope, all temperatures are given in degrees Celsius.

The following abbriviations are used:

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

DMF = N,N-dimethylformamide

TMG = tetramethylguanidine

AMCA = 7-amino-3-methoxymethyl-3-cephem-4-carboxylic acid

Determination of the diasterisomeric content A and B in a compound of formula III, I and cefpodoxim proxetil may be carried out by HPLC, e.g. analogously, as described in Pharmacopeial Forum, Vol. 23, No. 4, p. 4388 ff (1997), from which a diastereoisomeric ratio (B/A+B) and (A/A+B) may be calculated.

Example 1

a) 7-amino-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(isopropoxycarbonyloxy)ethyl ester

A suspension of 30 g of AMCA in 300 ml of acetone is mixed with 18.6 g of DBU and stirred for 15 minutes at room temperature. The solution obtained is cooled to ca. 0° and mixed over the course of ca. 15 minutes with 261 g of a 14% toluene solution of 1-iodoethylisopropyl carbonate. Stirring is continued fro ca. 4 hours at ca. 0° and the solution obtained is poured onto a mixture of 600 ml of water and 21 ml of conc. HCl. The pH of the mixture obtained is adjusted to ca. 1.0. The aqueous phase is extracted with 200 ml of hexane, mixed with 700 ml of ethyl acetate and a pH of ca. 8.2 is adjusted by addition of 5N NaOH. A two-phase system is obtained and the organic phase is extracted with an aqueous saturated NaCl solution, dried over $MgSO_4$, and filtered. A solution of 7-amino-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(isopropoxycarbonyloxy)ethyl ester in ethyl acetate is obtained. Diastereoisomeric ratio B/(A+B) = 0.49.

b) 7-[2-(2-formylaminothiazol-4-yl)-2-(Z)-(methoxyimino)acetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(isopropoxycarbonyloxy)ethyl ester

A solution of 37.4 g of 7-amino-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(isopropoxycarbonyloxy)ethyl ester with a diastereoisomeric ratio B/(A+B) of 0.49 in 689 ml of ethyl acetate is cooled with ice water. At a temperature of ca. 2-3°, 0.105 mols of Z-(2-formamidothiazol-4-yl)-methoxyimino-acetyl chloride hydrochloride are added in portions over the course of ca. 25 minutes, and the mixture obtained is stirred for ca. further 10 minutes. The pH is simultaneously adjusted to ca. 6.5 to 7.3 by addition of a solution of 18.48 g of sodium bicarbonate in 345 ml of water. Stirring is continued for ca. 1 hour. A two phase system is formed and the phases are separated; the organic phase is mixed with 350 ml of water and the pH of the mixture obtained is adjusted to ca. 7.4 by addition of a saturated sodium bicarbonate solution. The phases formed are separated and the organic phase is washed with 350 ml of water, mixed with 117 ml of DMF and concentrated by evaporation on a rotary evaporator at 40°/100 mbar until no further ethyl acetate is distilling off. An evaporation residue is obtained containing 7-[2-(2-formylaminothiazol-4-yl)-2-(Z)-(methoxyimino)acetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(isopropoxycarbonyloxy)ethyl ester in a diastereoisomeric ratio (B/A+B) of 0.49.

The evaporation residue is divided into portions. 7-[2-(2-formylaminothiazol-4-yl)-2-(Z)-(methoxyimino)acetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(isopropoxycarbonyloxy)ethyl ester is precipitated as follows:

Portions, 37 g each, of the evaporation residue are treated with the amount of ethanol as set out under "ml ethanol" in TABLE 1 below, and, over the course of ca. one hour, the amount of water as set out under "ml water" in TABLE 1 below is added dropwise whilst stirring. 7-[2-(2-formylaminothiazol-4-yl)-2-(Z)-(methoxyimino)acetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(isopropoxycarbonyloxy)ethyl ester precipitates. The suspension obtained is stirred for ca. further 30 minutes at room temperature, the precipitate is isolated, (isolation capability characteristic as set out in TABLE 1; "very good" means that the precipitate is very easily filterable, "good" means that the precipitate is easily filterable, "average" means that the precipitate is filterable and "poor" means that the precipitate is badly filterable) below through a suction filter, washed with water and dried over phosphorus pentoxide overnight at 40-45° in a drying chamber. 7-[2-(2-formylaminothiazol-4-yl)-2-(Z)-(methoxyimino)-acetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(isopropoxycarbonyloxy)ethyl ester in a diastereoisomeric ratio (B/A+B) as set out in TABLE 1 below is obtained:

TABLE 1

experiment	ml ethanol	ml water	diastereoisomeric ratio (B/A+B)	isolating capability
A	58.5	292.5	0.508	good
B	58.5	146.2	0.524	average
C	58.5	117	0.541	average
D	74	292.5	0.512	very good
E	74	370	0.508	very good
comparison	0	370	0.491	poor

c) 7-[2-(2-aminothiazol-4-yl)-2-(Z)-(methoxyimino)acetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(isopropoxycarbonyloxy)ethyl ester

5 g of each of the compounds obtained according to experiments A to E and comparison experiment as set out in TABLE 1 above, are added to a mixture of 35 ml of methanol and 0.6 ml of conc. sulphuric acid. The mixture is stirred for ca. 90 minutes and slowly added during ca. 25 minutes to a mixture of 2.1 g of sodium bicarbonate and 400 ml of water. 7-[2-(2-aminothiazol-4-yl)-2-(Z)-(methoxyimino)acetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(isopropoxycarbonyloxy)ethyl ester precipitates. The suspension obtained

is stirred for ca. one hour and the precipitate is isolated through a suction filter, washed with water and dried over phosphorus pentoxide overnight at ca. 35° in a vacuum. 7-[2-(2-aminothiazol-4-yl)-2-(Z)-(methoxyimino)acetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(isopropoxycarbonyloxy)ethyl ester (cefpodoxime proxetil) is obtained in a diastereoisomeric ratio (B/A+B) as set out in TABLE 2 below:

TABLE 2

experiment	diastereoisomeric ratio (B/A+B)
A	0.511
B	0.528
C	0.544
D	0.515
E	0.526
comparison	0.493

Example 2

a) Vilsmeier activation of Z-(2-formamidothiazol-4-yl)-methoxyimino)-acetic acid

A mixture of 200 ml of ethyl acetate and 54 ml of DMF is cooled to ca. -10°, treated with 10.06 ml phosphoroxychloride (0.11 mol) and stirred for ca. 1 hour at ca. -10°. The mixture obtained is cooled to ca. -15° and 26.36 g (0.115 mol) of Z-(2-formamidothiazol-4-yl)-methoxyimino)-acetic acid are added. The mixture obtained is stirred for ca. 1 hour at ca. -10° and cooled to ca. -25° and contains (Vilsmeier) activated Z-(2-formamidothiazol-4-yl)-methoxyimino)-acetic acid.

b) 7-[2-(2-formylaminothiazol-4-yl)-2-(Z)-(methoxyimino)acetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(isopropoxycarbonyloxy)ethyl ester

33.6 g of sodium bicarbonate in 748 ml of water are added to 558 ml of a solution of 0.105 mol of 7-amino-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(iso-propoxycarbonyloxy)-ethyl ester, obtained analogously as described in Example 1 a), diastereoisomeric ratio (B/A+B) below 0.5, at a temperature of below ca. 5° and further 228 ml of ethyl acetate are added to the mixture obtained. To the mixture obtained the mixture obtained in step a) is added dropwise at a temperature of below 5° within ca. one hour. The temperature is kept below 4°. The mixture obtained (pH 6.2) is stirred for ca. 30 minutes. A two-phase system is obtained, the phases are separated and the organic phase is washed with 370 ml of water. The pH of the organic phase is adjusted to 7.1 by addition of an aqueous sodium

bicarbonate solution. The mixture obtained is stirred for ca. 15 minutes and a two-phase system is obtained. The phases are separated and the organic phase is treated with 188 ml of water and 10 ml of 5M aqueous sulphuric acid. The mixture obtained is stirred for ca. 15 minutes and the phases obtained are separated. The organic phase is washed with ca. 200 ml of water and mixed with 117 ml of N,N-dimethylacetamide. The mixture obtained is concentrated in vacuo (rotovapor, 40°/100 mbar) until no further ethyl acetate is distilling off. 7-[2-(2-formylaminothiazol-4-yl)-2-(Z)-(methoxyimino)acetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(isopropoxycarbonyloxy)ethyl ester in a diastereoisomeric ratio (B/A+B) of 0.49 is obtained.

The evaporation residue is divided into portions and 7-[2-(2-formylaminothiazol-4-yl)-2-(Z)-(methoxyimino)acetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(isopropoxycarbonyloxy)ethyl ester is precipitated analogously as described in Example 1 b), but using 33.8 g portions of the evaporation residue instead of 37 g and using an amount of ethanol as set out in TABLE 3 below and an amount of water as set out in TABLE 3 below instead of amounts as set out in TABLE 1 above. 7-[2-(2-formylaminothiazol-4-yl)-2-(Z)-(methoxyimino)acetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(isopropoxy-carbonyloxy)ethyl ester in a diastereoisomeric ratio (B/A+B) and (A/A+B) as set out in TABLE 3 below is obtained:

TABLE 3

experiment	ml ethanol	ml water	diastereoisomeric ratio (B/A+B)	diastereoisomeric ratio (A/B+A)
A	58.5	292.5	0.503	0.497
B	58.5	146	0.518	0.482
C	58.5	117	0.538	0.462
D	0	370	0.497	0.503

Example 3

a) 7-amino-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(isopropoxycarbonyloxy)ethyl ester

A suspension of 30 g of AMCA in 300 ml of acetone is mixed with 14,2 g of TMG and stirred for 20 minutes at room temperature. The solution obtained is cooled to ca. 0° and mixed over the course of ca. 5 minutes with a solution of 38.0 g of 1-iodoethylisopropyl carbonate in 250 ml of toluene. Stirring is continued for ca. 4 hours at ca. 0° and the

solution obtained is poured onto a mixture of 600 ml of water and 20 ml of conc. HCl. The pH of the mixture obtained is adjusted to 1.0. The aqueous phase is extracted with 200 ml of toluene, mixed with 500 ml of methylene chloride and a pH of ca. 8.2 is adjusted by addition of 5N NaOH. A two-phase system is obtained; the organic phase is extracted with water and dried over $MgSO_4$. $MgSO_4$ is filtrated off and washed with with 50 ml of methylene chloride. 590 ml of a solution of 7-amino-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(isopropoxycarbonyloxy)ethyl ester in methylene chloride are obtained (content: 62 g/l). Diastereoisomeric ratio B/(A+B) = 0.48; and (A/A+B) = 0.52.

b) Vilsmeier activation of Z-(2-formamidothiazol-4-yl)-methoxyimino)-acetic acid

Is carried out analogously as described in Example 2 a) but using 100 ml of methylene chloride instead of 200 ml of ethyl acetate, 27 ml of DMF instead of 54 ml and 13.18 g instead of 26.36 g of (2-N-formylamino-thiazol-4-yl)-methoxyimino)-acetic acid. (Vilsmeier) activated Z-(2-formamidothiazol-4-yl)-methoxyimino)-acetic acid is obtained.

c) 7-[2-(2-formylaminothiazol-4-yl)-2-(Z)-(methoxyimino)acetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(isopropoxycarbonyloxy)ethyl ester

Is carried out analogously as described in Example 2 b) but

- using 1 6.8 g of sodiumbicarbonate instead of 33.6 g in 374 ml of water instead of 748 ml of water and adding the mixture to 317 ml of a solution obtained according to example 3 a), containing 0.0525 mol 7-amino-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(iso-propoxycarbonyloxy)ethyl ester; and
- adding 73 ml of methylene chloride instead of 228 ml of ethyl acetate;
- and adding the mixture obtained to the mixture containing (Vilsmeier) activated (2-N-formylaminothiazol-4-yl)- methoxyimino)-acetic acid obtained according to Example 3 b) instead to a mixture obtained according to Example 2 a); and
- using half of the amounts of solvents, water, acid and base after the first phase separation than described in Example 2 b) after the first phase separation, but using DMF instead of dimethylacetamide.

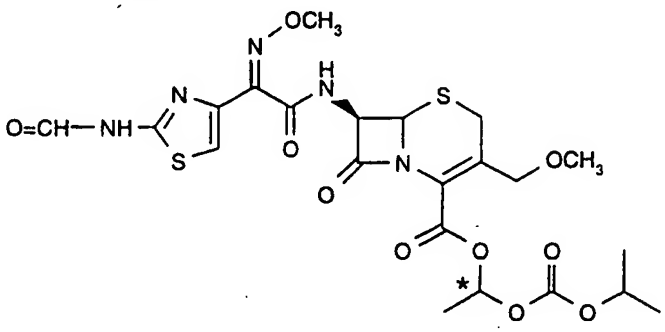
7-[2-(2-formylaminothiazol-4-yl)-2-(Z)-(methoxyimino)acetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(isopropoxycarbonyloxy)ethyl ester in a diastereoisomeric ratio (B/A+B) of 0.47 is obtained.

To 32.9 g of the evaporation residue are added 58.5 ml of ethanol. To the mixture obtained 105 ml of water are added dropwise. 7-[2-(2-formylaminothiazol-4-yl)-2-(Z)-(methoxy-imino)acetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(isopropoxycarbonyloxy)-ethyl ester in a diastereoisomeric ratio (B/A+B) of 0.50 is obtained.

To 32.9 g of the evaporation residue 370 ml of water is added dropwise. 7-[2-(2-formylaminothiazol-4-yl)-2-(Z)-(methoxyimino)acetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(isopropoxycarbonyloxy)ethyl ester in a diastereoisomeric ratio (B/A+B) of 0.475 is obtained.

Patent Claims

1. A process for the adjustment of the diastereoisomeric ratio (B/A+B) , wherein B is the more apolar of the two diastereoisomers, of a mixture of diastereoisomers of a compound of formula



I

the diastereoisomers being with respect with the carbon atom marked with a star in formula I, comprising treating a mixture of diastereoisomers of a compound of formula I with alcohol and water.

2. A process according to claim 1 comprising adjusting a diastereoisomeric ratio (B/A+B) to 0.5 to 0.6

3. A process according to any preceding claim, comprising treating a mixture of diastereoisomers of a compound of formula I in an additive with alcohol and water.

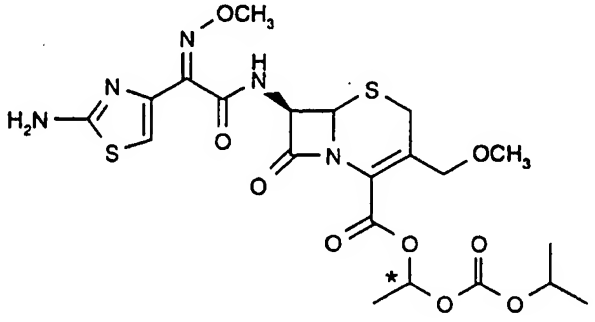
4. A process according to any preceding claim, comprising treating a mixture of diastereoisomers of a compound of formula I in a compound selected from an organic amide, an urea, an imidazolidinone or a pyrimidinone.

5. A process according to any preceding claim comprising selecting the alcohol from (C_{1-6})alcohols.

6. A process wherein a 10 to 50 % (w/w) solution of a mixture of diastereoisomers of a compound of formula I in an additive is treated with alcohol and water.

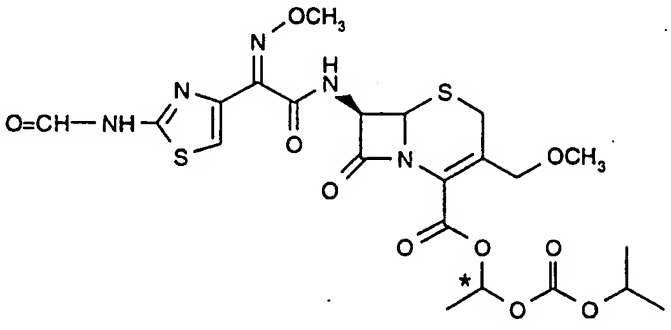
7. A process according to any preceding claim comprising treating a mixture of diastereoisomers of a compound of formula I with 3 ml to 10 ml alcohol and 10 ml to 30 ml water per gram of a compound of formula I.

8. A process for the production of a mixture of diastereoisomers of cefpodoxime proxetil of formula



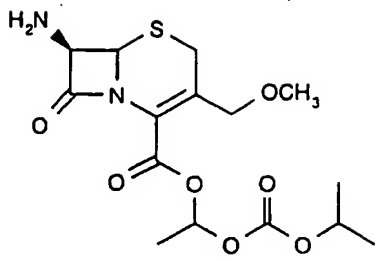
II

in a diastereoisomeric ratio (B/A+B), wherein B is the more apolar of the two diastereoisomers, of 0.5 to 0.6, the diastereoisomers being with respect with the carbon atom marked with a star in formula II, comprising producing a mixture of diastereoisomers of a compound of formula



I

by acylating a compound of formula



III

with activated Z-(2-formamidothiazol-4-yl)-methoxyimino acetic acid, treating a mixture of diastereoisomers of a compound of formula I obtained according to any one of claims 1 to 6 and splitting off the formyl group from the amino group attached to the thiazolyl group.

9. A process according to claim 8, wherein a compound of formula III is produced by esterifying 7-amino-3-methoxymethyl-3-cephem-4-carboxylic acid with a compound of formula

$$X\text{-}CH\text{-}(CH_3)\text{-}O\text{-}CO\text{-}O\text{-}CH(CH_3)_2$$

wherein X denotes a leaving group.

10. A process for the production of a mixture of diastereoisomers of cefpodoxim proxetil of formula II as defined in claim 8 in a diastereoisomeric ratio (B/A+B), wherein B is the more apolar of the two diastereoisomers, of 0.5 to 0.6, the diastereoisomers being with respect with the carbon atom marked with a star in formula II, characerized by the follwing steps

i) esterifying 7-amino-3-methoxymethyl-3-cephem-4-carboxylic acid with a compound of formula

$$X\text{-}CH\text{-}(CH_3)\text{-}O\text{-}CO\text{-}O\text{-}CH(CH_3)_2$$

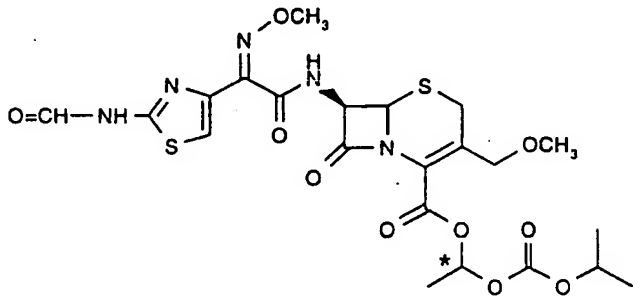
wherein X denotes a leaving group;

ii) acylating the amine group in position 7 of the ring system of a compound of formula III obtained in step i) with activated (2-N-formylamino-thiazol-4-yl)-methoxyimino acetic acid;

iii) adding a compound selected from an organic amide, an urea, an imidazolidinone or a pyrimidinone to a reaction mixture obtained in step ii) and evaporating off a solvent used in the acylation step, and

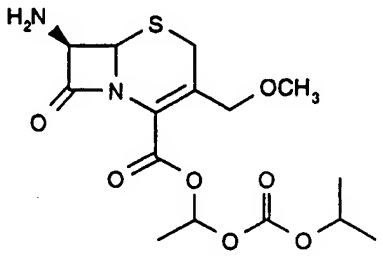
iv) treating the evaporation residue obtained in step iii) with alcohol and water.

11. A process for the isolation of 7-[2-(2-formylaminothiazol-4-yl)-2-(Z)-(methoxyimino)-acetamido]-3-methoxymethyl-3-cephem-4-carboxylic acid-1-(isopropoxy-carbonyloxy)-ethylester (as a diastereoisomeric mixture) of formula



I

e.g. after the reaction of the compound of formula



III

with activated Z-2-(methoxyimino)-2-(2-formylaminothiazol-4-yl)-acetic acid in a solvent, characterised in that to the solution of the compound of formula I is added an organic amide, a urea, 1,3-dimethyl-2-imidazolidinone (DMEU) or 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), the solvent is subsequently removed by evaporation and the residue of evaporation is mixed with water/alcohol.

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/EP 99/00057

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D501/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 531 875 A (HOECHST AG) 17 March 1993 see the whole document	1-11
A	CHEMICAL ABSTRACTS, vol. 125, no. 22, 25 November 1996 Columbus, Ohio, US; abstract no. 284616, HAMAURA T. ET AL.: "Gel formation of cefpodoxime proxetil" XP002102142 see abstract & S.T.P. PHARMA SCI., vol. 5, no. 4, 1995, pages 324-331,	1-11
A	US 4 486 425 A (NAKAO H. ET AL.) 4 December 1984 see claims	1-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 May 1999	21/05/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chouly, J

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/EP 99/00057

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 531875 A	17-03-1993	AU 647307 B	17-03-1994
		AU 2218392 A	11-03-1993
		CA 2077562 A	08-03-1993
		CN 1070405 A,B	31-03-1993
		CZ 282320 B	11-06-1997
		EG 20237 A	31-05-1998
		FI 923966 A	08-03-1993
		HR 920310 A	31-08-1994
		HU 64544 A	28-01-1994
		IL 103064 A	05-12-1996
		JP 2667943 B	27-10-1997
		JP 5213969 A	24-08-1993
		MX 9205081 A	01-03-1993
		NO 302122 B	26-01-1998
		NZ 244224 A	27-04-1995
		PL 171644 B	30-05-1997
		SK 276192 A	06-05-1998
		RU 2075480 C	20-03-1997
		US 5550232 A	27-08-1996
		US 5614623 A	25-03-1997
		US 5461043 A	24-10-1995
US 4486425 A	04-12-1984	JP 1336735 C	11-09-1986
		JP 57169489 A	19-10-1982
		JP 61001074 B	13-01-1986
		JP 1058192 B	11-12-1989
		JP 1570557 C	25-07-1990
		JP 57206687 A	18-12-1982
		JP 57059894 A	10-04-1982
		AT 19403 T	15-05-1986
		AU 547984 B	14-11-1985
		AU 7578181 A	08-04-1982
		CA 1171404 A	24-07-1984
		EP 0049118 A	07-04-1982
		FI 813038 A,B,	31-03-1982
		IE 53177 B	17-08-1988
		MX 9203566 A,B	01-09-1992
		PH 18740 A	16-09-1985
		US 4716158 A	29-12-1987
		CA 1172248 A	07-08-1984
		EP 0049119 A	07-04-1982
		EP 0134420 A	20-03-1985
		FI 813037 A,B,	31-03-1982
		PH 16994 A	04-05-1984
		US 4483855 A	20-11-1984